FORM PTO-1390 (REV 10-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: CV-0275

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09719183

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/03951	7 June 1999	9 June 1998

TITLE OF INVENTION: Use of a Wound Dressing in the Treatment of Acute Wounds

APPLICANT(S) FOR DO/EO/US: Kreis, Robert W.; Vloemans, Jos; Du Pont, Johannes,S.; Hoekstra, Matthias,J.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. [ ] The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [x] is attached hereto (required only if not communicated by the International Bureau).
   b. [ ] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [x] Other items or information:

International Publication No. WO99/64079

International Preliminary Examination Report with Annexes (2 sheets)

APPLICATION NO. (if known, see 37 CFR 1.5) 09/771918	INTERNATIONAL APPLICATION NO. PCT/EP99/03951	ATTORNEY'S DOCKET NUMBER CV-0275

17. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	8 - 20 =		X $18.00	$	
Independent claims	6 - 3 =	3	X $80.00	$ 240.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	$ 270.00	
TOTAL OF ABOVE CALCULATIONS =				$1370.00	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$	
SUBTOTAL =				$1370.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$1370.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$1370.00	
				Amount to be refunded:	$
				charged:	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 02-3869 in the amount of $ 1,370.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-3869. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Theodore R. Furman, Jr.

NAME

30,942

REGISTRATION NUMBER

#3

Docket No. CV0275

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re

Application of : Kreis et al.

Serial No. : 09/719183

Filed : December 8, 2000

For : Use of a Wound Dressing in the Treatment of Acute Wounds

Box Non-fee Amendment
Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

S I R :

Before examining the present application, please enter the new claims 9-12 shown below. Please charge any fees to Deposit Account No. 02-3869.

Add New Claims

9. In a method for the treatment of an acute wound which method involves the step of placing a skin graft or biological dressing over said acute wound,

the improvement comprising substituting for said skin graft or biological dressing a dressing comprising highly absorbent fibers selected from the group consisting of alginates, viscose, modified cellulose, cellulose, polyester, polypropylene and co-polymers thereof, pectin, chitosan, hyaluronic acid or mixtures thereof, which dressing adheres to the wound while allowing outgrowth of the wound epithelium during treatment.

10. The method of claim 9 wherein said acute wound is a burn.

11. The method of claim 9 wherein the dressing is non-occlusive.

12. The method of claim 9 wherein the dressing comprises modified cellulose fibers which can absorb at least 25 g/g of deionized water.

REMARKS

Applicants have added new claims 9-12 to the present case. Consideration of all the claims 1-12 is earnestly solicited.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited in the US mails as first class mailing, addressed to Assistant Commissioner for Patents, Washington, D.C. 20231 on January 4, 2001.

Signed by Blake Bolinger

USE OF A WOUND DRESSING IN THE TREATMENT OF ACUTE WOUNDS

This invention relates to the use of a wound dressing for the treatment of burns and other acute wounds and in particular the use of a dressing as a replacement for a biological dressing in the treatment of an acute wound.

Acute wounds which result in loss of skin, such as burns, require treatment in a variety of ways depending on size, severity and location. For instance a burn in which only the outer layer of skin is burned over a small percentage of the total skin surface can be treated with first aid measures in the home. There are many kinds of dressing available for these types of burns.

With burns in which perhaps all the layers of skin are damaged, and sometimes fat, nerve, muscle and tendon are involved or where a large percentage of the total skin surface is damaged it is usually necessary to use some form of skin graft or biological dressing to cover the wound and aid healing.

It is not always possible to take skin grafts from the patient (autograft) due to the extent of burning. In such circumstances biological dressings are the only alternative. Such dressings have many functions and take many forms. Some of their functions include preventing desiccation of the wound surface, decreasing evaporative water loss, decreasing heat loss, reducing bacterial proliferation, decreasing wound pain, protecting exposed tendons and nerves, and enhancing healing. Examples of biological dressings include naturally occurring

tissues such as cutaneous allografts, cutaneous xenografts or amniotic membranes; skin substitutes such as synthetic laminates, collagen based composites or collagen based dermal analogs; and culture derived tissue such as cultured autologous keratinocytes and fibroblast seeded dermal analogs.

Biological dressings can also be used as temporary covers over wounds that are subsequently covered by culture derived grafts and over wounds that have been treated with cutaneous widely expanded mesh grafts or culture derived grafts which leave open wound areas to achieve wound closure.

Biological dressings are sophisticated and therefore tend to be expensive and can carry the same risks of cross-contamination that are encountered with blood and blood products.

There therefore exists a need for a dressing that can be used to treat acute wounds, which performs in a similar manner to a biological dressing but mitigates the disadvantages of high cost and risk of contamination encountered with biological dressings.

Surprisingly we have found that certain wound dressings known for use in other treatments, such as the treatment of chronic wounds, can behave like a biological dressing and can reduce the need for autograft.

Accordingly the invention provides the use of a wound dressing for the preparation of a substitute for a biological dressing for use in the treatment of acute wounds and in particular the

treatment of wounds which contain epithelial remnants like partial thickness burns.

Such wound dressings do not have the disadvantages of high cost and cross contamination that may be encountered with biological dressings.

We have found that a wound dressing, to be suitable as a substitute for a biological dressing preferably is adherent to the wound without preventing the outgrowth of the epithelium. This is truly surprising since conventional wisdom teaches that wound dressings should not adhere to the acute wound and many known dressings are provided with measures to avoid adherence such as being impregnated with paraffin or being coated with silicone. We have found that an adherent dressing has advantages over the prior art dressings which allow the dressing to be used in those situations where a biological dressing would otherwise be used.

We have also found that wound dressings suitable as replacements for biological dressings preferably promote the migration of enzymes, neutrophils, fibroblasts and cellular debris into the dressing. Whilst not wishing to be bound by theory we believe that this migration, which we term as "vertical wicking", modulates the inflammatory response of the wound and contributes to successful healing of the wound.

Accordingly the invention provides the use of a wound dressing for the preparation of a substitute for a biological dressing for use in the treatment of acute wounds by adhering to the wound and providing conditions conducive to epithelial

outgrowth.

According to a further aspect, the invention provides the use of a wound dressing for the preparation of a substitute for a biological dressing for use in the treatment of acute wounds and particularly partial thickness burns by promoting vertical wicking into the dressing and thereby modulating inflammatory response.

In particular we have found that certain fibrous wound dressings are suitable for use in the present invention. The wound contact layer is fibrous and can comprise fibres of alginate, viscose, modified cellulose, cellulose, polyester, polypropylene and co-polymers thereof, pectin, chitosan fibres, hyaluronic acid fibres or other polysaccharide fibres or fibres derived from gums. Most preferred are highly absorbent fibres such as, modified cellulose fibres as described in WO93/12275 to Courtaulds Plc or WO 94/16746 to Courtaulds Plc and alginate fibres as described in WO 94/17227 to E.R. Squibb and Sons. By "highly absorbent" with respect to the fibre it is meant that they can absorb at least 25 g/g of deionized water. The fibres for use in the wound layer may also be mixed or blended to form a composite layer or may be fibres made of a mixture of any of the above ingredients. Preferably fibrous wound dressings include those described in WO94/16746 to Courtaulds Plc which discloses wound dressings made from carboxymethyl cellulose filaments.

It is particularly surprising that a fibrous dressing has this effect because biological dressings are occlusive in order to provide a barrier to bacteria. A fibrous dressing has an open

structure and therefore would not be expected to behave like a biological dressing.

A wound dressing made from carboxymethyl cellulose filaments is marketed as Aquacel® ex ConvaTec for use in the treatment of chronic wounds such as ulcers or pressure sores. We have observed that when Aquacel® is used on burns it exhibits surprising behaviour in that it adheres to the wound bed without blocking epithelial outgrowth. This type of behaviour would usually only be seen with a biological dressing such as allograft.

In the context of the present invention, biological dressings are: naturally occurring tissues such as cutaneous allografts, cutaneous xenografts or amniotic membranes; skin substitutes such as synthetic laminates, collagen based composites or collagen based dermal analogs; and culture derived tissue such as cultured autologous keratinocytes and fibroblast seeded dermal analogs.

Preferably the wound dressing of the present invention is used on acute wounds which are forming exudate. These tend to be partial thickness burns.

The invention will now be illustrated by way of the following non-limiting examples.

Example 1

Comparison of Aquacel with a biological dressing on second degree burns

Dressing materials used for the treatment of second degree burns ideally fulfill a number of demands. In addition to pain reduction, prevention of dehydration and infection, minimising the risk of hypertrofic scarring is an important feature. Cadaver allograft skin provided by the Euro Skin Bank was applied to the wound bed of second degree burns on the day of the burn or the first day post burn. In approximately 60% of burns treated the allograft became adherent to the wound, thereby reducing the risk of infection, regulated fluid loss and dried out to form a crust as wound healing was in progress. After 14 days the allograft was removed to reveal pale pink skin which had no signs of an inflammation reaction.

Aquacel® was used on 58 patients with second degree burns. It was applied to the wound on the first day post burn and in 80% to 90% of burns treated became adherent to the whole wound surface. Aquacel® dried out to form a crust as wound healing progressed and was easily peeled off once the wound had healed. Patients reported no pain or disruption of the newly formed skin. The healed skin had a stable, pale pink appearance with no signs of inflammation.

These results show the similarity in action of Aquacel® to allograft skin. They also show that the incidence of Aquacel® becoming fully adherent to the wound was greater than that with allograft skin which makes Aquacel® a more reliable treatment for wounds than allograft skin.

Example 2

Partial thickness wounds were made on the back of male Wistar rats. The wounds were covered with Aquacel and fixed in place with silk tape. After 3 to 7 days the rats were sacrificed and the wound tissues frozen in liquid nitrogen so that cryosections could be prepared. The cryosections were stained with haematoxilin-eosine so that the wound healing process could be evaluated. Specific immuno-histological sections were prepared to identify macrophages.

During the healing process, Aquacel® adhered very well to the wounds. After four days, Aquacel had the form of a moist gel. Once re-epithelialization was complete, the Aquacel® became dry and could be easily removed.

The cryosections showed that the fibres of Aquacel® had fully swelled leaving no interfiber spaces. This suggests that Aquacel® had vertically wicked the wound exudate away from the wound along with cellular debris and enzymes. We believe that this property of vertical wicking creates an environment where the inflammatory response of the wound is modulated and this provides optimal conditions for the outgrowth of the epithelium and wound healing.

This theory is supported by the fact that there were no signs of infection in the wound and bacteria were not observed in the cryosections.

Example 3

Use of Aquacel as a temporary cover over excised and skin transplanted wounds

Patients with extensive burns are often treated with autologous expanded mesh skin transplants. As these are susceptible to desiccation and infection the wound area is "closed" by the use of split skin allografts over the autologous transplants. Allografts are often not available and have the disadvantages of cost and contamination risk. As an alternative to allografts, synthetic biological dressings have been used but these often disrupt the outgrowth of the epithelium, a phenomenon known as blocking.

In several patients it was observed that the excision of burned tissue and transplantation with either autologous skin micrografts or skin meshgrafts, could be combined with Aquacel® as a temporary covering material. With Aquacel® no blocking of the outgrowth of the epithelium was observed.

These results show the superior performance of Aquacel® when used as a replacement for a biological dressing.

Claims

1) Use of a wound dressing for the preparation of a substitute for a biological dressing for use in the treatment of acute wounds requiring the use of a biological dressing, the wound dressing comprising highly absorbent fibres.

2) Use of a wound dressing for the preparation of a substitute for allograft skin for use in the treatment of acute wounds requiring the use of allograft skin, the wound dressing comprising highly absorbent fibres.

3) Use of a wound dressing for the preparation of an adherent temporary cover for use in the treatment of acute wounds requiring a temporary cover, the wound dressing comprising highly absorbent fibres.

4) Use of a wound dressing for the preparation of a substitute for a biological dressing for use in the treatment of acute wounds by adhering to the wound and providing conditions conducive to epithelial outgrowth, the wound dressing comprising highly absorbent fibres.

5) Use of a wound dressing for the preparation of a substitute for a biological dressing for use in the treatment of acute wounds by promoting vertical wicking into the dressing, thereby modulating inflammatory response, the wound dressing comprising highly absorbent fibres.

6) A wound dressing for use in the treatment of burns which promotes vertical wicking into the dressing and thereby modulates inflammatory response, the wound dressing comprising highly absorbent fibres.

7) Use of a wound dressing as claimed in any preceding claim, the wound dressing comprising fibres that can absorb at least 25g/g of deionized water.

8) Use of a wound dressing as claimed in claim 6 wherein the fibres are modified cellulose fibres.

Attorney Docket No. CV-275 #4

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed for which a patent is sought on the invention Use of a Wound Dressing in the Treatment of Acute Wounds the specification of which

[ ] is attached hereto
[x] was filed on December 8, 2000 as Application Serial No. 09/719,183

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business to the Patent and Trademark Office connected therewith: Theodore R. Furman, Jr., Reg. No. 30,942; Stuart E. Krieger, Reg. No. 28,731. Address all correspondence to Theodore R. Furman, Jr. c/o Bristol-Myers Squibb Company, 100 Headquarters Park Drive, Skillman, New Jersey 08558. Telephone (908) 904-2372.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

PRIORITY FOREIGN APPLICATION(S)

Number	Country	Filed (day/month/year)	Priority Claimed (Yes or No)
PCT/EP99/03591	PCT	07/JUNE/1999	YES

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application S.N.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1.00

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